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Dated 26 March 2004

Patents Form 1/77

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1/77
25JUN03 E817502-1 D00524
P01/7700 0.00-0314695.8

Request for grant of a patent

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1.	Your reference	4-33220P1	
2.	Patent application number *(The Patent Office will fill in this part)*	24 JUN 2003	0314695.8
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)*		7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic compounds	
5.	Name of your agent *(If you have one)*		
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROA ISLEWORTH MIDDLESEX TW7 6NH	Novartis Pharmaceutica UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	1800001	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

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Continuation sheets of this form	
Description	8
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co.

Date: 24th June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. S. Schnerr** **020 8560 5847**

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O-)Pro}-DPhg-DTrp-Lys-Tyr(4-Bzl)-Phe], in free form, salt form or protected form. Phg means -HN-CH(C_6H_5)-CO- and Bzl means benzyl.

These compounds in free form, salt form or protected form are referred to hereinafter as "compounds of the invention".

Due to short half-life and proteolytic degradation of the somatostatin analogues of the present invention, systemic delivery, e.g. parenteral administration, is highly desirable. However, parenteral administration may be very painful at the site of administration, especially in repeated administration.

It has now been found that parenteral compositions comprising a compound of the invention, and tartaric acid show particularly interesting properties, e.g. good tolerability and high stability.

A compound of the invention in protected form corresponds to a somatostatin analogue wherein at least one of the amino groups is protected and which by deprotection leads to a compound of formula II, preferably physiologically removable. Suitable amino protecting groups are e.g. as disclosed in "Protective Groups in Organic Synthesis", T. W. Greene, J. Wiley & Sons NY (1981), 219-287, the contents of which being incorporated herein by reference. Example of such an amino protecting group is acetyl.

A compound of the invention may exist e.g. in free or salt form. Salts include acid addition salts with e.g. inorganic acids, polymeric acids or organic acids, for example with hydrochloric acid, acetic acid, lactic acid, aspartic acid, benzoic acid, succinic acid or pamoic acid. Acid addition salts may exist as mono- or divalent salts, e.g. depending whether 1 or 2 acid equivalents are added. Preferred salts are the lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt and the pamoate monosalt.

The compounds of the invention may be prepared in accordance with conventional methods.

In a first aspect, the present invention provides a parenteral composition comprising a compound of the invention and tartaric acid.

According to the invention, typically the concentration of the compound of the invention in the composition of the invention is from about 0.05 to about 1 mg per ml composition, particularly 0.1 to 1 mg/ml.

Conveniently, the ratio of the compound of the invention to tartaric acid is about 0.001 to about 2 weight in weight, preferably about 0.05 to about 0.6.

The amount of the compound of the invention in the composition of the invention is from about 0.005% to about 0.1% based on a total weight of the formulation.

Preferably, the tartaric acid is in fine crystalline form. More preferably, crystalline D(-) or L(+) tartaric acid is used. The amount of tartaric acid is preferably from about 0.01% to about 1.5% w/w of the formulation, preferably about 0.01% to about 0.3%, more preferably about 0.15%. Preferably, the molarity of tartaric acid in the final composition is about 10 mM.

In accordance with the present invention, in addition to the tartaric acid and a compound of the invention, the pharmaceutical composition preferably comprises also a basic component selected and added to the composition in such a way that the pH of the tartaric acid buffered pharmaceutical composition is adjusted to a pH of about 4 to about 4.5, preferably about 4.2.

Preferably, the basic component is a base, e.g. sodium hydroxide or potassium hydroxide, or a basic salt e.g. sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate, or potassium carbonate. Preferably, the basic component is added in such an amount that the resulting pharmaceutical composition has a pH buffered as indicated above.

Preferably, the pharmaceutical composition of the invention is water based.

The composition of the invention may further comprise a tonicity agent such as mannitol, sodium chloride, glucose, dextrose, sucrose, or glycerins. Preferably, the tonicity agent is mannitol.

The amount of tonicity agent is chosen to adjust the isotonicity of the composition of the invention, e.g. mannitol preferably may be from about 1% to about 5% by weight of the composition, preferably about 4.95%. Conveniently, mannitol is present in a ratio mannitol to tartaric acid of about 20 to about 40, preferably about 33.

The compositions of the invention may contain additional excipients commonly employed in parenteral compositions in order to provide the required stability and therapeutic efficacy. Excipients may include e.g. an antioxidant or a preserving agent.

Antioxidants may be employed to protect the active agent from oxidative degradation particularly under the accelerated conditions of thermal sterilisation. Antioxidants may be selected from any of those compounds known in the art. Similarly, the amount of antioxidant

employed can be determined using routine experimentation. Preferably, the compositions of the invention do not contain an antioxidant.

A preserving agent, e.g. phenol, may preferably be added to the composition when it is formulated as multidose vials, cartridges or syringes. Preferably, the compositions of the invention do not contain a preserving agent.

Reference is made to the extensive literature on the subject for these and other excipients and procedures mentioned herein, see in particular Handbook of Pharmaceutical Excipients, Second Edition, edited by Ainley Wade and Paul J. Weller, American Pharmaceutical Association, Washington, USA and Pharmaceutical Press, London; and Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete edited by H.P. Fiedler, 4th Edition, Editio Cantor, Aulendorf and earlier editions which are incorporated herein by reference.

Preferably, the composition of the invention contains as active ingredient only compound of the invention, e.g. the compound of formula II.

Procedures which may be used to prepare the compositions of the invention may be conventional or known in the art or based on such procedures e.g. those described in L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, H. Sucker et al, Pharmazeutische Technologie, Thieme, 1991, Hager's Handbuch der pharmazeutischen Praxis, 4th Ed. (Springer Verlag, 1971) and Remington's Pharmaceutical Sciences, 13th Ed., (Mack Publ., Co., 1970) or later editions.

Typically, the compound of the invention, the tartaric acid and and optionally the other ingredients as mentioned in the desired amount are dissolved in an aqueous solvent, preferentially in water for injection, and the pH is adjusted with the base. The resulting solution may then be diluted with water to make it up to the final desired volume. The resulting solution may be filtered through a sterile filter, e.g. a Millipak® filter. Preferably, during above preparation oxygen (air) is displaced from contact with the solution of the compound of the invention. This is usually carried out by purging with, e.g. nitrogen, a container holding the solution. The pharmaceutical composition may be packed under carbon dioxide or other inert gas to prevent degradation, preferably under carbon dioxide, e.g. charged into vials, e.g. glass vials, ampoules, e.g. glass ampoules, or syringes, e.g. prefilled syringes, and steam or heat sterilized.

The solution may be freeze-dried by a conventional method under aseptic conditions to give a powder for injection which may be used to reconstitute the desired solution for parenteral administration shortly before administration by mixing the powder with the desired amount of solvent e.g. with water for injection.

The compositions of the invention are useful

a) for the prevention or treatment of disorders with an aetiology comprising or associated with excess GH-secretion and/or excess of IGF-1 e.g. in the treatment of acromegaly as well as in the treatment of type I or type II diabetes mellitus, especially complications thereof, e.g. angiopathy, diabetic proliferative retinopathy, diabetic macular edema, nephropathy, neuropathy and dawn phenomenon, and other metabolic disorders related to insulin or glucagon release, e.g. obesity, e.g. morbid obesity or hypothalamic or hyperinsulinemic obesity,

b) in the treatment of enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrom, inflammatory diseases, e.g. Grave's Disease, inflammatory bowel disease, psoriasis or rheumatoid arthritis, polycystic kidney disease, dumping syndrom, watery diarrhea syndrom, AIDS-related diarrhea, chemotherapy-induced diarrhea, acute or chronic pancreatitis and gastrointestinal hormone secreting tumors (e.g. GEP tumors, for example vipomas, glucagonomas, insulinomas, carcinoids and the like), lymphocyte malignancies, e.g. lymphomas or leukemias, hepatocellular carcinoma as well as gastrointestinal bleeding, e.g variceal oesophagial bleeding,

c) for the prevention or treatment of angiogenesis, inflammatory disorders as indicated above including inflammatory eye diseases, macular edema, e.g. cystoid macular edema, idiopathic cystoid macular edema, exudative age-related macular degeneration, choroidal neovascularization related disorders and proliferative retinopathy,

d) for preventing or combating graft vessel diseases, e.g. allo- or xenotransplant vasculopathies, e.g. graft vessel atherosclerosis, e.g. in a transplant of organ, e.g. heart, lung, combined heart-lung, liver, kidney or pancreatic transplants, or for preventing or treating vein graft stenosis, restenosis and/or vascular occlusion following vascular injury, e.g. caused by catherization procedures or vascular scraping procedures such as percutaneous transluminal angioplasty, laser treatment or other invasive procedures which disrupt the integrity of the vascular intima or endothelium,

e) for treating somatostatin receptor expressing or accumulating tumors such as pituitary tumors, e.g. Cushing's Disease, gastro-enteropancreatic, carcinoids, central nervous system, breast, prostatic (including advanced hormone-refractory prostate cancer),

ovarian or colonic tumors, small cell lung cancer, malignant bowel obstruction, paragangliomas, kidney cancer, skin cancer, neuroblastomas, pheochromocytomas, medullary thyroid carcinomas, myelomas, lymphomas, Hodgkins and non-Hodgkins lymphomas, bone tumours and metastases thereof, as well as autoimmune or inflammatory disorders, e.g. rheumatoid arthritis, Graves disease or other inflammatory eye diseases.

Preferably, the compositions of the invention are useful in the treatment of acromegaly and cancer, e.g. Cushing's Disease.

The activity and characteristics of the compositions of the invention may be indicated in standard clinical or animal tests.

Appropriate dosage of the composition of the invention will of course vary, e.g. depending on the condition to be treated (for example the disease type or the nature of resistance), the drug used, the effect desired and the mode of administration.

When given continuously, an effective amount of drug may be given in two or three doses spread over time such as by parenteral administration, e.g. intravenous drip, intramuscular or subcutaneous injection(s), or subcutaneous infusion, e.g. continuous subcutaneous infusion, preferably subcutaneous injection or infusion, with the total daily dose being spread across the portion or the entire administration period. When given by subcutaneous injection, it is most preferably administered from 3 times per week up to 3 times a day, preferably twice a week up to once or twice daily. A compound of the invention may also be administered in the form of e.g. a subcutaneous bolus injection.

The composition of the invention preferably is suitable for subcutaneous administration.

After injection, the composition of the invention is locally well tolerated. Particularly, the parenteral administration of a composition of the invention, e.g. subcutaneous injection, leads to mild to no burning sensation at the injection site.

In addition to the good local tolerance after injection, the composition of the invention exhibits good stability characteristics. For example, less than 2.5% of degradation products were found after 4 weeks storage at 60°C. For example, if stored with light protection at 2°C to 8°C, the compositions of the invention are stable over 24 months. Particularly good stability may be observed with the diaspartate salt of Compound A.

In general, satisfactory results are obtained on administration, e.g. subcutaneous administration, at dosages on the order of from about 0.01 to about 1.2 mg, preferably from about 0.1 to about 0.6 mg of the compound of the invention per injection or about 0.001 to about 0.009 mg per kg animal body weight per day, administered once or in divided doses up to 4 times per day. Suitable daily dosages for patients are thus in the order of about 0.1 mg to about 0.6 mg of a compound of the invention, e.g. a compound of formula II, e.g. Compound A.

The following Examples serve to illustrate the invention.

Examples 1 to 4:

Tartaric acid and mannitol are dissolved in water for injection, while the solution is purged with nitrogen. Then diaspartate salt of compound A is added, the solution is adjusted with sodium hydroxide to pH 4.20 and water for injection up to 1.0 ml is added. Under aseptic conditions, the solution is filtered through a Millipak-200 ® sterile filter with a pore size ≤0.22 µm, filled into ampoules and sterilized by autoclaving..

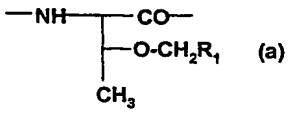
	Ex 1	Ex 2	Ex 3	Ex 4
diaspartate salt of Compound A (corresponding amount of Compound A)	0.315 (0.251)	0.472 (0.376)	0.786 (0.627)	1.415 (1.129)
tartaric acid crystalline	1.501	1.501	1.501	1.501
mannitol	49.500	49.500	49.500	49.500
sodium hydroxide 1N for injection	ad pH 4.20	ad pH 4.20	ad pH 4.20	ad pH 4.20
water for injection	ad 1ml	ad 1ml	ad 1ml	ad 1ml

Claims

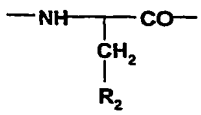
1. A pharmaceutical composition for parenteral administration comprising a somatostatin analogue comprising the amino acid sequence of formula I

-(D/L)Trp-LYs-X_1 -X_2 - I

wherein X_1 is a radical of formula (a) or (b)



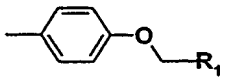
(a)



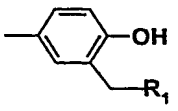
(b)

wherein R_1 is optionally substituted phenyl,

R_2 is $-Z_1-CH_2-R_1$, $-CH_2-CO-O-CH_2-R_1$,



or

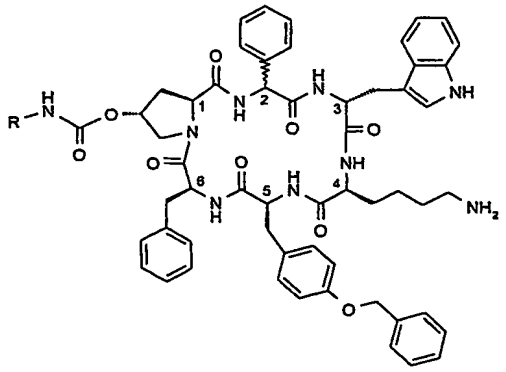


wherein Z_1 is O or S, and

X_2 is an α-amino acid having an aromatic residue on the C_α side chain, or an amino acid unit selected from Dab, Dpr, Dpm, His,(Bzl)HyPro, thienyl-Ala, cyclohexyl-Ala and t-butyl-Ala, the residue Lys of said sequence corresponding to the residue Lys^9 of the native somatostatin-14

in free form, salt form, or protected form and tartaric acid.

2. A composition according to claim 1 wherein the somatostatin analogue is a compound of formula II



II

wherein the configuration at C-2 is (R) or (S) or a mixture thereof, and

wherein R is NR_1R_2-C_{2-6}alkylene or guanidine-C_{2-6}alkylene, and each of R_1 and R_2 independently is H or C_{1-4}alkyl,
in free form, salt form or protected form.

3. A composition according to claim 1 or 2 wherein the compound of the somatostatin analogue is in aspartate di-salt form.

4. A composition according to any preceding claim wherein the composition is adjusted to a pH of about 4 to about 4.5.

5. A composition according to any preceding claim further comprising a tonicity agent.

6. A composition according to claim 5 wherein the tonicity agent is mannitol.

7. A composition for parenteral administration substantially as hereinbefore described or defined.

8. Use of a pharmaceutical composition according to any one of claims 1 to 7 for the preparation of a medicament for acromegaly or cancer.

9. A method of treating acromegaly or cancer in a subject in need thereof which comprises administering a pharmaceutical composition according to any one of claims 1 to 7 to the subject.

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